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Synthesis and Properties of Novel Chiral Ionic Liquids from L-Proline

Hong-Shuai Gao,[A] *Zhi-Guo Hu,*[A] *Jian-Ji Wang,*[A,C] *Zhao-Fa Qiu,*[A] *and Feng-Qiu Fan*[B]

[A]Department of Chemistry, Henan Key Laboratory of Environmental Pollution Control, Henan Normal University, Xinxiang, Henan 453007, China.

[B]Department of Chemical and Biomolecular Engineering, Johns Hopkins University, Baltimore, MD 21218, USA.

[C]Corresponding author. Email: jwang@henannu.edu.cn

A novel class of chiral ionic liquids with chiral cations directly derived from natural L-proline has been synthesized and their physical properties such as melting point, thermal degradation, and specific rotation have been characterized. Further, their potential use in chiral recognition was demonstrated by studying interactions with racemic Mosher's acid salt.

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Introduction

Room-temperature ionic liquids (RTILs) are low-melting salts that melt at temperatures below 100°C, representing a new class of non-molecular ionic solvents.[1,2] Because of their unique physical and chemical properties, they have potential as greener alternatives to volatile organic solvents. Among them, chiral ionic liquids (CILs) are particularly attractive for their potential applications in asymmetric organic reactions,[3,4] chiral discrimination,[5–7] and optical resolution of racemic mixtures.[8] However, studies on CILs are still in a preliminary stage, only a few kinds of CILs have been synthesized,[9,10] and their synthesis required rather expensive reagents and elaborate synthetic schemes. Amino acids are the most abundant natural chiral materials and are not expensive. Several groups have reported the synthesis of novel CILs with chiral cations from amino acids;[10] surprisingly, they tend to use these amino acids only as precursors for the multi-step synthesis of more complex materials. To our knowledge, reports on the preparation of chiral cations directly from natural materials are few.[11–16] At the same time, it has been reported that some asymmetric carbon atoms in CILs may undergo racemization after a certain time.[17] L-Proline is a representative amino acid with the chiral centre in the pyrrole ring, so the CILs derived from it cannot be racemized easily. Moreover, because L-proline is a good chiral catalyst,[18,19] it is expected that the CILs based on L-proline may be used as catalyst or solvent for asymmetric organic reactions. Herein, we report the synthesis and characterization of a novel class of CILs using the commercially available L-(−)-proline as starting material.

Results and Discussion

In this context, 14 novel CILs with chiral cations derived directly from natural L-proline were synthesized following Scheme 1. On treatment of L-proline with $SOCl_2$ in methanol or ethanol, the L-proline methyl ester and the L-proline ethyl ester were obtained respectively in relatively high yield (>90%). *N*-Alkylation of the esters using methyl iodide or ethyl iodide or ethyl bromide occurred smoothly in CH_3CN to produce **1a**, **2a**, **2b**, **3a**, **4a**, and **4b** (yields from 78 to 90%).

Next, we investigated the exchange of counteranions. *N*,*N*-Dimethyl-L-proline ethyl ester nitrate and tetrafluoroborate, and *N*,*N*-diethyl-L-proline ethyl ester nitrate and tetrafluoroborate were obtained in almost quantitative yields through the anion exchange of the L-proline ester iodide salt with $AgNO_3$ or $AgBF_4$. Similarly, the anion exchange of **1a**, **2a**, and **3a** with $NaPF_6$ produced L-proline ester hexafluorophosphorate in 72–75% yield. All of these were characterized by ^1H and ^{13}C NMR spectroscopy, infrared (IR), differential scanning calorimetry (DSC), thermogravimetry (TG), time-of-flight mass spectroscopy (TOF-MS), and elemental analysis.

Results for all the CILs are summarized in Table 1. The products are named using L-Pro as a symbol for L-proline, and using the first carbon atom to represent the ester group and the second carbon atom to represent the *N*-alkyl group. For example, *N*,*N*-dimethyl-L-proline ethyl ester iodide is denoted by L-Pro-C_2-C_1I and *N*,*N*-diethyl-L-proline methyl ester iodide by L-Pro-C_1-C_2I. It can be seen from Table 1 that the melting points of L-proline ester halogenated salts are higher, but they decrease greatly when the anion is replaced by NO_3^-, BF_4^-, and PF_6^-. When the anions are the same, melting points of the CILs decrease in the order: *N*,*N*-diethyl-L-proline ethyl ester CILs > *N*,*N*-dimethyl-L-proline methyl ester CILs > *N*,*N*-dimethyl-L-proline ethyl ester CILs, indicating the important role of the size of the cation in determining the physical properties of ionic liquids. This is similar to the situation found with imidazolium ionic liquids. Most of the CILs are found to be thermally stable up to 200°C, even higher than 300°C, which is much higher than the minimum 100°C criterion described by Wasserscheid for CIL.[20]

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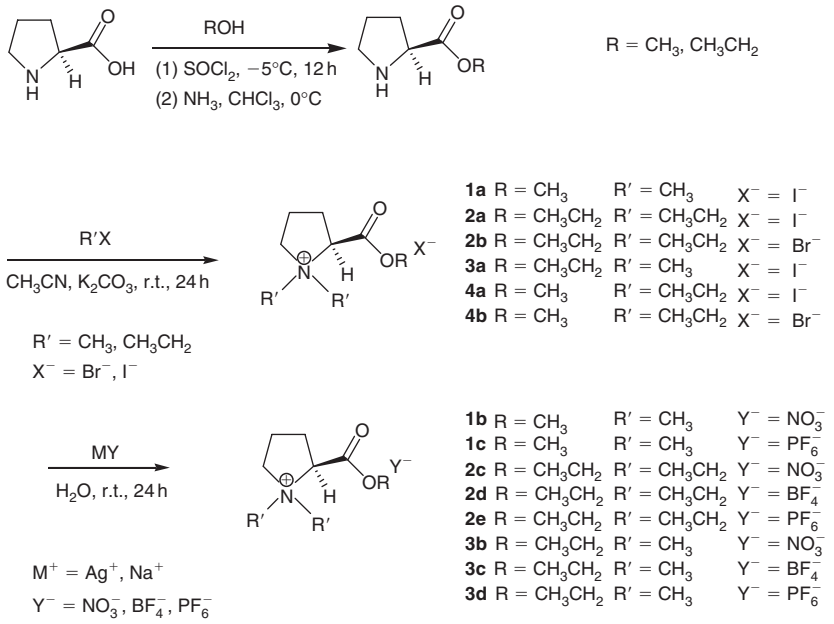

Scheme 1. Synthesis of L-proline-based ionic liquids.

Table 1. Properties of L-proline-based ionic liquids

No.	Chiral ionic liquids	T_m [°C][A]	T_d [°C][B]	$[\alpha]_D^{20\,C}$	Yield [%]
1a	L-Pro-C_1-C_1I	102	201	−15.5	90
1b	L-Pro-C_1-C_1NO_3	59	215	−20	87
1c	L-Pro-C_1-C_1PF_6	47	299	−13	72
2a	L-Pro-C_2-C_2I	129	195	−32.5	83
2b	L-Pro-C_2-C_2Br	71	185	−35.2	78
2c	L-Pro-C_2-C_2NO_3	62	216	−36.5	81
2d	L-Pro-C_2-C_2BF_4	79	323	−31.5	76
2e	L-Pro-C_2-C_2PF_6	94	338	−17	73
3a	L-Pro-C_2-C_1I	109	188	−20.5	86
3b	L-Pro-C_2-C_1NO_3	18	210	−25.3	85
3c	L-Pro-C_2-C_1BF_4	35	324	−24	80
3d	L-Pro-C_2-C_1PF_6	32	339	−15	75
4a	L-Pro-C_1-C_2I	116	188	−34.3	84
4b	L-Pro-C_1-C_2Br	99	193	−37	73

[A] Melting points (T_m) were determined by differential scanning calorimetry, heating at 10°C min^{-1} under nitrogen.
[B] Decomposition temperature (T_d) was determined by thermogravimetric analysis, heating at 10°C min^{-1} under nitrogen.
[C] Solution in CH_3OH and molarity of CIL, 2.0 mol L^{-1}.

Their thermal stability increases in the order: *N*,*N*-diethyl-L-proline ester CILs < *N*,*N*-dimethyl-L-proline ester CILs for the same anions, and halogenate < NO_3^- < BF_4^- < PF_6^- for the same cations. These results suggest that the thermal decomposition temperature of these CILs can be tuned by the alkyl chain length of cation and the type of anion. In addition, good rotation was observed for all the CILs synthesized in the present work, indicating that the chiralty of L-proline has been retained in the CILs. It was observed that the chirality of all the CILs, as shown in Table 1, remained unchanged even after 2 months or longer. This is different from some asymmetric carbon atoms in CILs that have been reported to undergo racemization after a certain time.[17]

To evaluate the chiral discrimination ability of the novel CILs, we investigated the diastereomeric interaction between **3a**, **3d** and racemic Mosher's acid salt by ^{19}F NMR spectroscopy.[5] When racemic Mosher's acid salt was dissolved in **3a** or **3d**, diastereomeric complexes were formed between the *N*,*N*-dimethyl-L-proline ethyl ester cation and racemic Mosher's acid anion. The CF_3 group of the racemic Mosher's acid salt remained in a chiral environment. The signal splitting for the two diastereomeric CF_3 groups could be attributed to the diastereomeric interaction (Fig. 1). It was also found that the concentration of the CIL has a significant influence on the extent of the Mosher's acid salt fluorine signal splitting.

Conclusions

Fourteen novel CILs have been synthesized and characterized. The synthetic scheme is simple and practical, and follows a general esterification and *N*-alkylation procedure, along with having commercial availability of the starting materials and favourable reaction conditions. In addition, these CILs have relatively high thermal stability (185–339°C) and the melting points of most of them are below 100°C. As a preliminary study, we have also shown their chiral discrimination abilities by investigating the diastereomeric interaction between **3a**, **3d** and racemic Mosher's acid salt. Research into future applications of these new CILs is in progress.

Experimental

General Methods

All reagents and solvents were of pure analytical grade purchased from commercial sources. Methanol and ethanol were purified by standard procedures. The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or CD_3COCD_3 on a Bruker 400 MHz spectrometer. All IR samples were taken as KBr plates. The spectra were recorded on a FTS-40 Fourier transform infrared spectrophotometer (BIU-RAD) with a resolution of 4 cm^{-1}. Melting points from the onset position were determined from the first heating cycle. Melting points were recorded on a Thermal Analysis DSC 6200 DSC with heating at 10°C min^{-1} under nitrogen. Decomposition temperatures (T_{dec}) were recorded on a Thermal

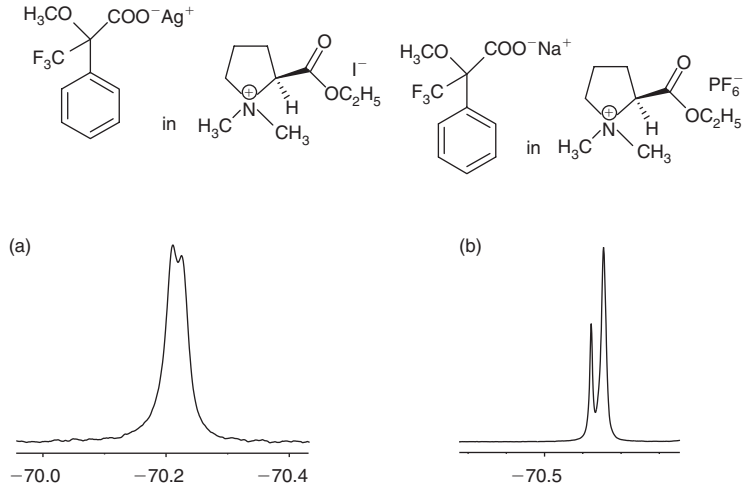

Fig. 1. ^{19}F NMR spectra of (a) racemic Mosher's acid silver salt in **3a**; (b) racemic Mosher's acid sodium salt in **3d**.

Analysis Tg/DTA 6300 at a heating rate of 10°C min^{-1} under nitrogen. Optical rotations were measured in a WZZ-1 automatic indication polarimeter.

N,N-*Dimethyl-L-proline Methyl Ester Iodide, L-Pro-C_1-C_1I* ***1a***

$SOCl_2$ (47 mL) was added dropwise slowly into a mixture of L-proline (30 g, 0.26 mol) and anhydrous methanol (300 mL) with vigorous stirring at −5°C. Then the mixture was stirred overnight at room temperature. The excess methanol and $SOCl_2$ were removed under reduced pressure and the residue was dissolved in $CHCl_3$ (300 mL) and cooled down to 0°C. After bubbling dry NH_3 into the solution for 2 h, the solid was filtered off, and the filtrate was concentrated under reduced pressure. After drying under vacuum at 50°C, the colourless liquid L-proline methyl ester was obtained (31 g, 92%). K_2CO_3 (13.8 g, 0.1 mol) was added into the mixture of L-proline methyl ester (12.9 g, 0.1 mol) and CH_3CN (150 mL). After stirring the mixture for 1.5 h at room temperature, CH_3I (15.5 mL) was added dropwise. One day later, the solid was filtered off, and the resulting liquid was concentrated under reduced pressure. The light yellow solid crude product L-pro-C_1-C_1I was recrystallized CH_3CHCl_3 until no *N*-methyl-L-proline methyl ester remained, then dried under vacuum at 50°C (25.6 g, 90%), mp 102°C. $[\alpha]_D^{20}$ −15.5 (*c* 2.0, CH_3OH). ν_{max} (KBr)/cm^{-1} 3386, 2958, 1743, 1440, 1246, 1007, 906. δ_H (400 MHz, D_2O) 4.47 (t, *J* 9.6, 1H, CH), 3.83 (s, 3H, CH_3), 3.58–3.79 (m, 2H, CH_2), 3.34 (s, 3H, CH_3), 3.11 (s, 3H, CH_3), 2.53–2.61 (m, 1H, CH_2), 2.37–2.47 (m, 1H, CH_2), 2.16–2.25 (m, 2H, CH_2). δ_C (100 MHz, D_2O) 167.2, 73.7, 68.2, 53.7, 52.5, 46.7, 24.5, 18.8. TOF-MS (ES+) *m/z* Calc. for $[C_8H_{16}NO_2]^+$ 158.2. Found 158.1. Calc. for $C_8H_{16}NO_2I$ C 33.7, H 5.7, N 4.9. Found C 33.5, H 5.6, N 5.0%.

N,N-*Dimethyl-L-proline Methyl Ester Nitrate, L-Pro-C_1-C_1NO_3* ***1b***

L-Pro-C_1-C_1I (3.41 g, 0.012 mol) and $AgNO_3$ (2.04 g, 0.012 mol) were separately dissolved in water (5 mL). After mixing the two solutions with vigorous stirring at room temperature for 12 h, the precipitate was filtered off, and the solvent was evaporated under vacuum. Drying under vacuum at 50°C, the waxy solid *N,N*-dimethyl-L-proline methyl ester nitrate was obtained (2.31 g, 87% yield), mp 59°C. $[\alpha]_D^{20}$ −20 (*c* 2.0, CH_3OH). ν_{max} (KBr)/cm^{-1} 3471, 3034, 2962, 1747, 1351, 1243, 1000, 963. δ_H (400 MHz, $CDCl_3$) 4.98 (t, *J* 9.6, 1H, CH), 3.93–3.99 (m, 2H, CH_2), 3.85 (s, 3H, CH_3), 3.54 (s, 3H, CH_3), 3.23 (s, 3H, CH_3), 2.68–2.72 (m, 1H, CH_2), 2.21–2.39 (m, 3H, CH_2CH_2). δ_C (100 MHz, $CDCl_3$) 167.3, 73.7, 68.6, 54.3, 52.9, 47.1, 25.7, 19.9. TOF-MS (ES+) *m/z* Calc. for $[C_8H_{16}NO_2]^+$ 158.2. Found 158.2. Calc. for $C_8H_{16}N_2O_5$ C 43.6, H 7.3, N 12.7. Found C 43.6, H 7.4, N 12.7%.

N,N-*Dimethyl-L-proline Methyl Ester Hexafluorophosphorate, L-Pro-C_1-C_1PF_6* ***1c***

L-Pro-C_1-C_1I (6.19 g, 0.0217 mol) and $NaPF_6$ (3.65 g, 0.0217 mol) were separately dissolved in water (10 mL). After mixing the two solutions with vigorous stirring at room temperature for 12 h, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water until no I^- salt remained and the solvent was evaporated under vacuum. After drying under vacuum at 50°C, the light yellow waxy solid *N,N*-dimethyl-L-proline methyl ester hexafluorophosphorate was obtained (4.74 g, 72%), mp 47°C. $[\alpha]_D^{20}$ −13 (*c* 2.0, CH_3OH). ν_{max} (KBr)/cm^{-1} 3671, 2976, 1733, 1381, 1264, 1046, 837. δ_H (400 MHz, CD_3COCD_3) 4.74 (t, *J* 9.6, 1H, CH), 3.88–4.05 (m, 2H, CH_2), 3.92 (s, 3H, CH_3), 3.58 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 2.59–2.74 (m, 2H, CH_2), 2.37–2.43 (m, 2H, CH_2). δ_C (100 MHz, CD_3COCD_3) 167.1, 74.4, 68.8, 53.8, 53.1, 47.3, 25.5, 19.7. TOF-MS (ES+) *m/z* Calc. for $[C_8H_{16}NO_2]^+$ 158.2. Found 158.2. Calc. for $C_8H_{16}F_6NO_2P$ C 31.7, H 5.3, N 4.6. Found C 31.5, H 5.1, N 4.5%.

N,N-*Diethyl-L-proline Ethyl Ester Iodide, L-Pro-C_2-C_2I* ***2a***

This compound was synthesized in the same manner as that described for L-Pro-C_1-C_1I using anhydrous ethanol (300 mL), and CH_3CH_2I (24.7 mL). Light yellow solid, 72%, mp 129°C. $[\alpha]_D^{20}$ −32.5 (*c* 2.0, CH_3OH). ν_{max} (KBr)/cm^{-1} 3462, 2985, 1740, 1384, 1240, 1019, 863. δ_H (400 MHz, CD_3COCD_3) 4.96 (t, *J* 8.2, 1H, CH), 4.35 (q, *J* 7.2, 2H, CH_2), 3.76–4.03 (m, 4H, CH_2, CH_2), 3.65 (q, *J* 7.3, 2H, CH_2), 2.67–2.76 (m, 1H, CH_2), 2.28–2.54 (m, 3H, CH_2CH_2), 1.44–1.52 (m, 6H, CH_3, CH_3), 1.35 (t, *J* 7.2, 3H, CH_3). δ_C (100 MHz, CD_3COCD_3) 167.2, 72.2, 63.7, 61.4, 56.4, 53.5, 26.4, 20.5, 14.2, 9.6, 9.4. TOF-MS

(ES+) *m/z* Calc. for $[C_{11}H_{22}NO_2]^+$ 200.3. Found 200.2. Calc. for $C_{11}H_{22}NO_2I$ C 40.4, H 6.8, N 4.3. Found C 40.4, H 6.8, N 4.3%.

N,N-*Diethyl-L-proline Ethyl Ester Bromide, L-Pro-C_2-C_2Br* ***2b***

This compound was synthesized in the same manner as that described for L-Pro-C_1-C_1I using anhydrous ethanol (300 mL), and CH_3CH_2Br (22.8 mL). Light yellow solid, 78%, mp 71°C. $[\alpha]_D^{20}$ −35.2 (*c* 2.0, CH_3OH). ν_{max} (KBr)/cm^{-1} 3427, 2986, 1737, 1471, 1237, 1020. δ_H (400 MHz, CD_3COCD_3) 4.99 (t, *J* 8.2, 1H, CH), 4.33 (q, *J* 7.4, 2H, CH_2), 3.77–4.08 (m, 4H, CH_2, CH_2), 3.64 (q, *J* 7.2, 2H, CH_2), 2.68–2.77 (m, 1H, CH_2), 2.38–2.52 (m, 3H, CH_2CH_2), 1.42–1.52 (m, 6H, CH_3, CH_3), 1.35 (t, *J* 7.2, 3H, CH_3). δ_C (100 MHz, CD_3COCD_3) 167.5, 72.3, 63.5, 61.5, 56.5, 53.3, 26.5, 20.5, 14.1, 9.5, 9.3. TOF-MS (ES+) *m/z* Calc. for $[C_{11}H_{22}NO_2]^+$ 200.3. Found 200.2. Calc. for $C_{11}H_{22}NO_2Br$ C 47.2, H 7.9, N 5.0. Found C 46.8, H 7.8, N 4.8%.

N,N-*Diethyl-L-proline Ethyl Ester Nitrate, L-Pro-C_2-C_2NO_3* ***2c***

This compound was synthesized in the same manner as that described for L-Pro-C_1-C_1NO_3 using L-Pro-C_2-C_2I (3.75 g, 0.012 mol). Light yellow solid, 81%, mp 62°C. $[\alpha]_D^{20}$ −36.5 (*c* 2.0, CH_3OH). ν_{max} (KBr)/cm^{-1} 3464, 2988, 1739, 1378, 1199, 1019. δ_H (400 MHz, $CDCl_3$) 4.75 (t, *J* 8, 1H, CH), 4.31 (q, *J* 7, 2H, CH_2), 3.44–3.92 (m, 6H, CH_2, CH_2, CH_2), 2.66–2.75 (m, 1H, CH_2), 2.19–2.41 (m, 3H, CH_2CH_2), 1.39–1.49 (m, 6H, CH_3, CH_3), 1.34 (t, *J* 7.2, 3H, CH_3). δ_C (100 MHz, $CDCl_3$) 167.3, 72.1, 63.9, 61.4, 56.5, 52.9, 26.7, 20.7, 14.7, 9.8, 9.4. TOF-MS (ES+) *m/z* Calc. for $[C_{11}H_{22}NO_2]^+$ 200.3. Found 200.2. Calc. for $C_{11}H_{22}N_2O_5$ C 50.4, H 8.5, N 10.7. Found C 50.3, H 8.3, N 10.6%.

N,N-*Diethyl-L-proline Ethyl Ester Tetrafluoroborate, L-Pro-C_2-C_2BF_4* ***2d***

This compound was synthesized in the same manner as that described for L-Pro-C_1-C_1NO_3 using L-Pro-C_2-C_2I (3.75 g, 0.012 mol), and $AgBF_4$ (2.34 g, 0.012 mol). Light yellow solid, 76%, mp 79°C. $[\alpha]_D^{20}$ −31.5 (*c* 2.0, CH_3OH). ν_{max} (KBr)/cm^{-1} 3564, 2993, 1739, 1379, 1062. δ_H (400 MHz, CD_3COCD_3) 4.68 (t, *J* 8, 1H, CH), 4.33 (q, *J* 7, 2H, CH_2), 3.55–3.84 (m, 6H, CH_2, CH_2, CH_2), 2.60–2.69 (m, 1H, CH_2), 2.34–2.53 (m, 3H, CH_2CH_2), 1.39–1.48 (m, 6H, CH_3, CH_3), 1.33 (t, *J* 7, 3H, CH_3). δ_C (100 MHz, CD_3COCD_3) 167.2, 72.0, 63.7, 61.0, 56.0, 53.2, 26.3, 20.4, 14.03, 9.0, 8.6. TOF-MS (ES+) *m/z* Calc. for $[C_{11}H_{22}NO_2]^+$ 200.3. Found 200.2. Calc. for $C_{11}H_{22}BF_4NO_2$ C 46.0, H 7.7, N 4.9. Found C 45.9, H 7.6, N 4.7%.

N,N-*Diethyl-L-proline Ethyl Ester Hexafluorophosphorate, L-Pro-C_2-C_2PF_6* ***2e***

This compound was synthesized in the same manner as that described for L-Pro-C_1-C_1PF_6 using L-Pro-C_2-C_2I (6.78 g, 0.0217 mol). Light yellow solid, 73%, mp 94°C. $[\alpha]_D^{20}$ −17 (*c* 2.0, CH_3OH). ν_{max} (KBr)/cm^{-1} 3462, 2994, 1735, 1261, 1039, 842. δ_H (400 MHz, CD_3COCD_3) 4.66 (t, *J* 8, 1H, CH), 4.33 (q, *J* 7.2, 2H, CH_2), 3.53–3.85 (m, 6H, CH_2, CH_2, CH_2), 2.57–2.67 (m, 1H, CH_2), 2.25–2.52 (m, 3H, CH_2CH_2), 1.39–1.46 (m, 6H, CH_3, CH_3), 1.29 (t, *J* 7.2, 3H, CH_3). δ_C (100 MHz, CD_3COCD_3) 167.2, 72.0, 63.7, 61.0, 55.9, 53.3, 26.3, 20.4, 14.0, 9.0, 8.6. TOF-MS (ES+) *m/z* Calc. for $[C_{11}H_{22}NO_2]^+$ 200.3. Found 200.2. Calc. for $C_{11}H_{22}F_6NO_2$ P C 38.3, H 6.4, N 4.1. Found C 38.0, H 6.4, N 3.9%.

N,N-*Dimethyl-L-proline Ethyl Ester Iodide, L-Pro-C_2-C_1I* ***3a***

This compound was synthesized in the same manner as that described for L-Pro-C_1-C_1I using anhydrous ethanol (300 mL). Light yellow solid, 86%, mp 109°C. $[\alpha]_D^{20}$ −20.5 (*c* 2.0, CH_3OH). ν_{max} (KBr)/cm^{-1} 3478, 3005, 1746, 1468, 1240, 1184, 1022, 863. δ_H (400 MHz, $CDCl_3$) 5.27 (t, *J* 9.6, 1H, CH), 4.77–4.79 (m, 1H, CH_2), 4.28 (q, *J* 4, 2H, CH_2), 4.10–4.17 (m, 1H, CH_2), 3.73 (s, 3H, CH_3), 3.29 (s, 3H, CH_3), 2.71–2.79 (m, 1H, CH_2), 2.35–2.45 (m, 3H, CH_2CH_2), 1.34 (t, *J* 9.2, 3H, CH_3). δ_C (100 MHz, $CDCl_3$) 166.5, 74.4, 68.8, 64.0, 53.1, 48.5, 25.6, 20.0, 14.9. TOF-MS (ES+) *m/z* Calc. for $[C_9H_{18}NO_2]^+$ 172.2. Found 172.2. Calc. for $C_9H_{18}NO_2I$ C 36.1, H 6.0, N 4.7. Found C 36.0, H 6.1, N 4.67%.

N,N-*Dimethyl-L-proline Ethyl Ester Nitrate, L-Pro-C_2-C_1NO_3* ***3b***

This compound was synthesized in the same manner as that described for L-Pro-C_1-C_1NO_3 using L-Pro-C_2-C_1I (3.58 g, 0.012 mol). Light yellow liquid, 85%, mp 18°C. $[\alpha]_D^{20}$ −25.3 (*c* 2.0, CH_3OH). ν_{max} (KBr)/cm^{-1} 3478, 2989, 1740, 1646, 1378, 1099, 1040, 831. δ_H (400 MHz, CD_3COCD_3) 4.91 (t, *J* 9.6, 1H, CH), 4.37 (q, *J* 7, 2H, CH_2), 3.91–4.06 (m, 2H, CH_2), 3.59 (s, 3H, CH_3), 3.34 (s, 3H, CH_3), 2.52–2.73 (m, 2H, CH_2), 2.29–2.39 (m, 2H, CH_2), 1.36 (t, *J* 5.6, 3H, CH_3). δ_C (100 MHz, CD_3COCD_3) 166.9, 74.2, 68.7, 63.5, 52.9, 47.1, 25.5, 19.7, 14.2. TOF-MS (ES+) *m/z* Calc. for $[C_9H_{18}NO_2]^+$ 172.2. Found 172.2. Calc. for $C_9H_{18}N_2O_5$ C 46.2, H 7.8, N 12.0. Found C 46.3, H 7.5, N 11.7%.

N,N-*Dimethyl-L-proline Ethyl Ester Tetrafluoroborate, L-Pro-C_2-C_1BF_4* ***3c***

This compound was synthesized in the same manner as that described for L-Pro-C_1-C_1NO_3 using L-Pro-C_2-C_1I (3.58 g, 0.012 mol), and $AgBF_4$ (2.34 g, 0.012 mol). Light yellow waxy solid, 80% yield, mp 35°C. $[\alpha]_D^{20}$ −24 (*c* 2.0, CH_3OH). ν_{max} (KBr)/cm^{-1} 3634, 2987, 1743, 1474, 1253, 1058, 849. δ_H (400 MHz, CD_3COCD_3) 4.74 (t, *J* 9.6, 1H, CH), 4.37 (q, *J* 7, 2H, CH_2), 3.82–4.02 (m, 2H, CH_2), 3.56 (s, 3H, CH_3), 3.33 (s, 3H, CH_3), 2.54–2.75 (m, 2H, CH_2), 2.33–2.41 (m, 2H, CH_2), 1.36 (t, *J* 7.2, 3H, CH_3). δ_C (100 MHz, CD_3COCD_3) 166.8, 74.2, 68.7, 63.5, 52.9, 47.1, 25.4, 19.63, 14.1. TOF-MS (ES+) *m/z* Calc. for $[C_9H_{18}NO_2]^+$ 172.2. Found 172.2. Calc. for $C_9H_{18}BF_4NO_2$ C 41.7, H 7.0, N 5.4. Found C 41.6, H 7.0, N 5.3%.

N,N-*Dimethyl-L-proline Ethyl Ester Hexafluorophosphorate, L-Pro-C_2-C_1PF_6* ***3d***

This compound was synthesized in the same manner as that described for L-Pro-C_1-C_1PF_6 using L-Pro-C_2-C_1I (3.58 g, 0.012 mol). Light yellow waxy solid, 75%, mp 32°C. $[\alpha]_D^{20}$ −15 (*c* 2.0, CH_3OH). ν_{max} (KBr)/cm^{-1} 3675, 2989, 1737, 1463, 1232, 1040, 838. δ_H (400 MHz, CD_3COCD_3) 4.67 (t, *J* 9.6, 1H, CH), 4.37 (q, *J* 5.4, 2H, CH_2), 3.89–4.02 (m, 2H, CH_2), 3.56 (s, 3H, CH_3), 3.32 (s, 3H, CH_3), 2.52–2.74 (m, 2H, CH_2), 2.31–2.39 (m, 2H, CH_2), 1.36 (t, *J* 7, 3H, CH_3). δ_C (100 MHz, CD_3COCD_3) 166.6, 74.4, 68.8, 63.6, 53.1, 47.2, 25.4, 19.7, 14.1. TOF-MS (ES+) *m/z* Calc. for $[C_9H_{18}NO_2]^+$ 172.2. Found 172.2. Calc. for $C_9H_{18}F_6NO_2P$ C 34.1, H 5.7, N 4.4. Found C 33.7, H 5.6, N 4.4%.

N,N-*Diethyl-L-proline Methyl Ester Iodide, L-Pro-C_1-C_2I* ***4a***

This compound was synthesized in the same manner as that described for L-Pro-C_1-C_1I using CH_3CH_2I (24.7 mL). Light yellow solid, 84%, mp 116°C. $[\alpha]_D^{20}$ −34.3 (*c* 2.0, CH_3OH). ν_{max} (KBr)/cm^{-1} 3456, 2982, 2909, 1740, 1457, 1232, 1037, 816. δ_H (400 MHz, CD_3COCD_3) 4.99 (t, *J* 9.6, 1H, CH), 3.78–4.03 (m, 4H, CH_2, CH_2), 3.90 (s, 3H, CH_3), 3.61–3.71 (m, 2H, CH_2), 2.67–2.77 (m, 1H, CH_2), 2.31–2.55 (m, 3H, CH_2CH_2), 1.44–1.52 (m, 6H, CH_3, CH_3). δ_C (100 MHz, CD_3COCD_3) 166.8, 71.2, 60.4, 55.5, 53.2, 52.7, 25.5, 19.6, 8.6, 8.4. TOF-MS (ES+) *m/z* Calc. for $[C_{10}H_{20}NO_2]^+$ 186.3. Found 186.2. Calc. for $C_{10}H_{20}NO_2I$ C 38.4, H 6.4, N 4.5. Found C 38.4, H 6.4, N 4.4%.

N,N-*Diethyl-L-proline Methyl Ester Bromide, L-Pro-C_1-C_2Br* ***4b***

This compound was synthesized in the same manner as that described for L-Pro-C_1-C_1I using CH_3CH_2Br (22.8 mL). Light yellow solid, 73%, mp 99°C. $[\alpha]_D^{20}$ −37 (*c* 2.0, CH_3OH). ν_{max} (KBr)/cm^{-1} 3413, 2989, 1741, 1454, 1248, 1014. δ_H (400 MHz, CD_3COCD_3) 4.90 (t, *J* 8, 1H, CH), 3.87 (s, 3H, CH_3), 3.75–3.98 (m, 4H, CH_2, CH_2), 3.56–3.68 (m, 2H, CH_2), 2.28–2.74 (m, 4H, CH_2CH_2), 1.39–1.49 (m, 6H, CH_3, CH_3). δ_C (100 MHz, CD_3COCD_3) 167.0, 71.1, 60.4, 55.4, 53.0, 52.4, 25.5, 19.7, 8.4, 8.1. TOF-MS (ES+) *m/z* Calc. for $[C_{10}H_{20}NO_2]^+$ 186.3. Found 186.2. Calc. for $C_{10}H_{20}NO_2Br$ C 45.1, H 7.6, N 5.3. Found C 44.9, H 7.4, N 5.2%.

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